***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

***39 CYCLE***

**Project proposal for a Sapienza PhD scholarship**

**Main research line**

**Title:** Cellular basis of the neurodegenerative dementia FENIB

**Supervisor:** Maria Elena Miranda Banos

[mariaelena.mirandabanos@uniroma1.it](mailto:mariaelena.mirandabanos@uniroma1.it)

<https://corsidilaurea.uniroma1.it/it/users/mariaelenamirandabanosuniroma1it>

**Summary**

Neuroserpin is one of the serpins (serin protease inhibitors), a conserved superfamily of proteins that inhibit serin proteases by a mechanism that requires a high structural flexibility, which renders serpin proteins very sensitive to point mutations that alter their folding. This molecular mechanism underlies a class of pathologies called the serpinopathies, in which point mutations cause serpin polymerisation and retention within the endoplasmic reticulum (ER). To date, six different mutations have been described in neuroserpin, a secreted serpin expressed mainly by neurons, which cause polymer formation and a rare but deadly type of neurodegeneration called FENIB. The neuronal toxicity caused by polymer accumulation inside the ER is still poorly understood. To address this, we have created a neuronal cell model of FENIB based on *in vitro* differentiation of neural progenitor cells; in this system, we have described for the first time an oxidative stress response in cells expressing the highly polymerogenic G392E variant of NS. These cells undergo apoptosis when the antioxidant defences are inhibited pharmacologically and show alterations in mitochondrial distribution that can be corrected with the use of antioxidant molecules. We have also observed alterations in neuronal morphology, suggesting a link between oxidative stress, mitochondrial dysfunction and cytoskeletal alterations in FENIB neurons that is currently under investigation in our group. This pathology is exceedingly rare and is probably underdiagnosed, particularly in elderly patients in which it may be attributed to other forms of dementia; aside from FENIB, mutations in the neuroserpin gene *SERPINI1* are now recognised as a risk factor for some types of epilepsy and dementia, and so *SERPINI1* has been included in sequencing panels designed to uncover dementia-related mutations. A high number of neuroserpin variants consisting in single nucleotide changes has been annotated in population databases, but their clinical significance is still unknown. We use our cell culture models of FENIB to assess the effects of novel mutations in neuroserpin and to better understand the molecular bases of FENIB.

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